What is the effect of a reduced sodium intake on blood pressure in children from birth to age 18 years?

Conclusion

A moderate body of evidence has documented that as sodium intake decreases, so does blood pressure in children, birth to 18 years of age.

Grade: Moderate

Overall strength of the available supporting evidence: Strong; Moderate; Limited; Expert Opinion Only; Grade not assignable For additional information regarding how to interpret grades, click here

Evidence Summary Overview

Of the 15 trials, 14 were randomized controlled clinical trials (RCTs) (Calabrese et al, 1985; Cooper et al, 1984; Gillum et al, 1981; Hofman et al, 1983; Howe et al, 1985; Howe et al, 1991; Lucas et al, 1988; Myers, 1989; Palacios et al, 2004; Pomeranz et al, 2002; Sinaiko et al, 1993; Trevisan et al, 1981; Tuthill and Calabrese, 1985; Whitten and Stewart, 1980). Five of theRCTs earned a positive quality rating (Gillum et al, 1981 Hofman et al, 1983; Howe et al; 1991 Sinaiko et al, 1993; Tuthill and Calabrese, 1985); and seven earned a neutral quality rating (Calabrese et al, 1985; Cooper et al, 1984; Howe et al, 1985; Myers, 1989, Palacios et al, 2004; Pomeranz et al, 2002; Whitten and Stewart, 1980). Two RCTs earned a negative quality rating (Lucas et al, 1988; Trevisan et al, 1981). One non-randomized controlled study (positive quality rating) was the largest and longest trial, a two-period cross-over study conducted in two boarding schools (Ellison et al, 1989). Results of these studies support the conclusion that a reduced sodium intake appears to lowerblood pressure in infants and children.

Four prospective studies also provided evidence that supported the conclusion statement. One was a 15-year follow-up study (Geleijnse et al, 1997, positive quality) of the infant study subjects in the RCT conducted by Hofman et al, 1983 in the Netherlands. Three additional studies were prospective longitudinal cohort studies (Geleijnse et al, 1990, positive quality; Brion et al, 2008, neutral quality; and Smith et al, 1995, negative quality).

Ten of the 14 RCTs achieved contrasts in sodium intake of 40% or more between treatment groups or periods (Cooper et al, 1984; Hofman et al, 1983; Howe et al, 1985; Howe et al, 1991; Lucas et al, 1988; Myers, 1989; Palacios et al, 2004; Pomeranz et al, 2002; Tuthill and Calabrese, 1985; Whitten and Stewart, 1980). Two other RCTs achieved contrasts of 7 to 12% (Calabrese et al, 1985; Trevisan et al, 1981); and two achieved less than a 2% difference between treatment groups (Gillum et al, 1981; Sinaiko et al, 1993). Although the extent of sodium reduction often appeared large, the data often came from dietary recalls or dietary histories, rather than 24-hour urine collections.

Additionally, 12 of the 15 intervention studies showed a decrease in systolic (SBP) and/or diastolic (DBP) blood pressure on the low sodium diet (Calabrese et al, 1985; Cooper et al, 1984; Ellison et al, 1989; Hofman et al, 1983; Howe et al, 1985; Howe et al, 1991; Myers, 1989; Palacios et al, 2004; Pomeranz et al, 2002; Sinaiko et al, 1993; Trevisan et al, 1981; Whitten and Stewart, 1980). In eight of those 12 intervention studies, the decrease was statistically significant for all, or a subset, of the study population (Calabrese et al, 1985; Ellison et al, 1989; Hofman et al, 1983; Howe et al, 1985; Myers, 1989; Pomeranz et al, 2002; Sinaiko et al, 1993; Trevisan et al, 1981). Three studies reported no change in blood pressure on a low sodium diet (Gillum et al, 1981; Lucas et al, 1988; Tuthill and Calabrese, 1985).

Results from two of the three prospective cohort studies tend to support the results of the intervention trials. Two studies (Brion et al, 2008; Geleijnse et al, 1990) involved prospective cohorts that were followed for seven years. In the study by Brion et al, 2008, higher sodium (Na) intake at four months of life (but not at seven months or seven years) was associated with increased SBP at seven years of age. This was consistent with a greater difficulty excreting a sodium load by infants under four months of age. In the cohort study by Geleijnse et al, 1990, a higher Na/K ratio was associated with a greater increase in slope of blood pressure (BP) change over time. In the infant cohort study by Smith et al, 1995 (negative quality), neither the contrast in sodium intake, nor the actual BP was provided. The authors indicated that in the multivariate analysis, the amount of salt added to the diet approached clinical significance

(P=0.0751).

The third prospective cohort study was a long term, 15-year follow-up study (Geleijnse et al, 1997, positive quality) of an RCT conducted among infants who participated in the initial trial between birth and six months of age. In this study, SBP and DBP at follow-up were still lower among children initially assigned to the low sodium diet during infancy. The difference for SBP was statistically significant (P<0.05) and for DBP was of borderline significance (P=0.08).

In aggregate, these data indicate that sodium reduction modestly lowers BP in infants and children. While the degree of BP lowering was usually small, in the range of -1 to -5mmHg, such an effect, if sustained over time, could translate into reduced BP in adults, as well as reduced prevalence of hypertension. Furthermore, if a reduced sodium intake blunts the age-related rise in BP in children, then the effects of sodium reduction will be greater than projected from these studies. Nonetheless, it must be acknowledged that most of the studies had one or more methodological limitations, particularly small sample size (and consequently inadequate statistical power), brief duration (typically less than one month), and inadequate or uncertain contrast in sodium intake.

Evidence summary paragraphs:

Brion et al, 2008 (neutral quality). This study was a prospective cohort study begun in infancy to examine the associations between sodium (Na) intake and blood pressure at age seven years. This study was conducted in England. Subjects included 533 children initially studied at four months of age, and 710 children studied at eight months of age, who were followed to seven years of age. Sodium intake was estimated from data collected from food diaries and information obtained from food manufacturers. Mean sodium intake at four months was 7.2mmol per day and 0.4% of children exceeded recommended levels for infant sodium intake. At eight months, mean Na intake was 23.1mmol per day and 73.0% of children exceeded recommended Na intake levels. Mean BP at seven years of age in children initially assessed at four and/or eight months of age was 98.4±9.4/56.4±6.7mmHg. Sodium intake at four months of age was positively associated with SBP at age seven years (P=0.02). Sodium intake at eight months of age and at seven years of age was not significantly associated with BP at age seven years, however. These findings are consistent with evidence that before the age of four months, infants are less able to excrete excess Na loads.

Calabrese EJ & Tuthill RW, 1985 (neutral quality). This study was a randomized, controlled, three-arm parallel trial that examined the effects on blood pressure of 12 weeks of a reduced sodium (Na) intake in children. The trial was conducted in the United States. Subjects were 171 children, mean age nine years. Trios of children matched by sex, school, and baseline BP were randomly assigned to one of three different types of water for cooking and drinking purposes. The Na concentration of bottled water was 10mg per L for the low-Na group and 110mg per L for the two high Na groups (water bottled directly from their own high Na concentration water distribution system; or water from the low Na concentration drinking water community with added sodium added up to 110mg per L). The final analysis was completed on 164 children. Sodium intake was estimated from monthly first morning urine specimens and from weekly 48-hour diet records kept by the children with help from parents and teachers. UNa from first-morning urine samples decreased from 141 to 128mmol per L in the low-salt group and increased from 121 to 124mmol per L in the control group. For all subjects combined, the low Na water intervention reduced SBP -0.80±0.80mmHg, and DBP -1.50±1.65mmHg. The decrease in BP was only significant for females however. Among females, SBP decreased over 12 weeks from 97.7±10.1 to 92.4±8.5mmHg, and DBP decreased from 56.1±9.2 to 47.4±11mmHg. None of the differences in UNa excretion were statistically significant over the study period for any group, and BP changes did not correlate with UNa excretion. Strengths of the study include the controlled intake of water sodium levels. Limitations of the study which could have influenced outcome include the use of spot urine samples rather than 24-hour samples to measure sodium excretion; lack of control over school lunch preparation; dietary assessment methodology of unknown validity (records kept by children); and lack of description of the statistical methods.

Cooper et al, 1984 (neutral quality). This study was a randomized, controlled, two period-crossover trial that examined the effects on BP of 24 days of a reduced sodium (Na) intake in adolescent children. The trial was conducted in the United States. Participants were 124 healthy adolescents (mean age 16 years) at a boarding school. During the low Na period, the intervention aimed to reduce the Na content the food service from 200 to 60mEq per 24-hours. The final analysis was completed on 113 children. Sodium intake was estimated from weekly timed overnight urine samples, and the Na content of foods consumed for 24 hours was analyzed for a random sub-sample of three students per week. Overnight UNa was reduced from 31 in the control group to 13mmol per eight hours in the group that received the reduced Na intervention. Analysis of foods found that the control diet contained ~110mEq Na per day (rather than the predicted 200mEq per day), and the intervention diet ~45mEq per day. Across all subjects there was a nonsignificant decrease in BP (SBP: -0.6±0.7mmHg and DBP: -1.4±1.0) associated with the reduced Na intervention (net of control). In those individuals with a BMI below the median (BMI<23kg/m^2), there was a statistically significant fall in SBP (P<0.05). A strength of the study was adherence to the diet in this institutional setting. Limitations of the study, which might lead to a spurious null result, include predicted sodium content of the control diet (110 vs. 200mEq per day); the short duration of intervention (24 days); and the lack of blinding of students as to their treatment groups.

Ellison et al, 1989 (positive quality). This study was a non-randomized, concurrently controlled, two-period crossover trial that examined the effects on blood pressure of six-months of a reduced sodium (Na) intake in adolescents. The trial was conducted in the United States. Participants were healthy adolescents (mean age 15 years) at two boarding schools, 341 subjects during the control school year, and 309 subjects during the low sodium (Na) intervention year. The intervention occurred in each boarding school during alternate school years. Sodium intake was estimated from food diaries, with an average of 4.5 food diaries per subject obtained during baseline and follow-up period. Food diaries showed that average salt intake was reduced by 15-20%. Students measured their own BP every week using an automatic BP device connected to a computer. Baseline BP was taken as the mean of all recordings obtained during four weeks at the beginning of the BP associated with the low-Na intervention: SBP -1.7mmHg (95% CI=-0.6, -2.9, P=0.003), and DBP -1.5mmHg (95% CI=-0.6, -2.5, P=0.002). There was no evidence of bias that would lead to a spurious association. Strengths of the study are the long term nature of the interventions (six month school year), the blinding of BP-readings from students; and adherence to the intervention via boarding school food service. A potential limitation is that order (control vs. reduced sodium intervention) was not randomized; however, because the unit of assignment was the school rather than individual, this is not a major problem.

Geleijnse JM et al, 1997 (positive quality). This study was a 15-year follow-up of an RCT that examined the effects on blood pressure of a low or normal sodium diet during the first six months of life. The follow-up study was conducted to determine if contrasting levels of Na intake in infancy are associated with BP differences in adolescence. This study was conducted in the Netherlands. In the infant study, 245 newborn infants were assigned to a normal-Na diet and 231 to a low-Na diet. Infants assigned to the low-Na group received formula that was reduced in Na compared to the normal-Na formula (6.3 vs. 19.2mmol Na per L). The Na intake of the normal-Na group was almost three times that of the low-Na group measured as total intake of Na calculated from the food consumed along with an allowance for breastfeeding based upon the Na in the mother's breast milk. In addition, Na intake was estimated from spot urine collections. Systolic BP was measured every month from the first week until the 25th week. At 25 weeks, SBP was 2.1mmHg lower in the low-Na group than in the normal Na group. The difference between the groups increased significantly during the first six months of life. In the 15-year adolescent follow-up study,167 children (71 low-Na; 96 high Na), or 35% of the original cohort were re-evaluated. Results showed that there was still a significant difference in BP at follow-up between children who were randomly assigned to receive a low-salt diet in infancy (SBP: 3.6 mmHg lower (95% CI, -6.6 to -0.5) and DBP: 2.2mmHg lower (95% CI, -4.5 to 0.2), compared to those who received the high salt infant diet. The in children who had been assigned to the low Na group (N=71) compared with the control group (N=96). This occurred despite the fact that infants went back to their usual salt intake when the double-blind trial stopped at six months of age. There was little evidence of bias that would lead to a spurious association. Strengths of the study include the long duration of follow-up after randomization and the approach to data analysis, which took into account potential confounders. A limitation of the study was the loss to follow-up of individuals who originally enrolled in the trial when they were infants. Overall, these findings suggest that sodium intake in infancy is an important determinant of BP later in life.

Geleijnse et al, 1990 (positive quality). This study was a prospective cohort study to examine the association of sodium and potassium intake with blood pressure during childhood. The study was conducted in the Netherlands. Participants were 233 children, aged 5.9 to 17.0 years of age, who were followed for seven years. Six annual overnight urine samples were collected to estimate 24-hour Na excretion, and slopes ofBP change over time were calculated. Results showed that mean SBP increased at a rate of 1.95mmHg per year. There was no significant association between sodium excretion and annual change in SBP (0.003mmHg per year per mmol of Na; 95% CI: -0.006 to 0.012). In contrast, higher potassium (K) excretion was associated with a lower age-related rise in SBP (-0.045mmHg per year per mmol of K; 95% CI: -0.069 to - 0.020)], while a higher Na/K ratio was associated with a greater rise in SBP (0.356mmHg per year per unit; 95% CI 0.069 to 0.642). Urinary electrolyte excretion was not associated with changes inDBP. Strengths of the study include the long term follow-up. Limitations include the relatively small number of participants for a cohort study and use of overnight urine collections to estimate 24-hour electrolyte intake.

Gillum RF et al, 1981 (positive quality). This study was a randomized, controlled, two-arm parallel trial that examined the effects on blood pressure of one-year of a reduced sodium intake in children. The trial was conducted in the United States. Participants were 80 public school children, ages six to nine years, with BP >95th percentile for age and sex but <130/90mmHg. During the low Na period, families received dietary counseling to lower Na intake to 70mEq per person per day. The final analysis was completed on 51 children (15 intervention; 36 controls). Sodium intake was estimated from urine collections and diet histories. Subjects reported 40% lower Na intake in dietary records. Twenty-four hour Na intake at one-year follow-up was significantly lower for active participants of the low-Na intervention group as compared to dropouts and controls (87 vs. 130 and 133mmol per 24-hours). Overnight UNa changed from 31 to 35mmol per 10 hours in the control group, and from 30 to 31 mmol per 10 hours in the intervention group. Overall, there was no significant difference in BP between the intervention and control groups. For the low Na intervention, net change in SBP was 3.00±2.61mmHg, and for DBP was 2.90±5.79mmHg. The BP changes did not correlate with changes in 24-hour Na excretion. Limitations of the study, which might lead to a spurious null result, include the high drop out rate of intervention families (21 of 41 families dropped out). Although the drop-outs occurred before the intervention started, it resulted in a significantly lower sample size, especially for the intervention group. In addition, 24-hour urinary Na excretion data were available for intervention children only.

Hofman A et al, 1983 (positive quality). This study was a randomized, double-blind parallel arm trial that examined the effects on blood pressure of two levels of sodium intake in infants during the first six months of life. The trial was conducted in the Netherlands. Two hundred forty-five newborn infants were assigned to a normal-Na diet and 231 to a low-sodium diet. Infants assigned to the low-Na group received formula that was reduced in Na compared to the normal-sodium formula (6.3 vs. 19.2 mmol Na per L). The Na intake of the normal-Na group was almost three times that of the low-Na group measured as total intake of sodium calculated from the food consumed along with an allowance for breastfeeding based upon the Na in the mother's breast milk. In addition, Na intake was estimated from spot urine collections. Systolic BP was measured every month from the first week until the 25th week. At 25 weeks, SBP was 2.1mmHg lower in the low-Na group than in the normal Na group. The difference between the groups increased significantly during the first six months of life. According to the authors these observations were in agreement with the view that Na intake is causally related to BP level. There was no evidence of bias that would lead to a spurious association. Strengths of the study include high follow-up rates and a large sample size, which compensated for the relatively few number of BP measurements (only one BP per month).

Howe PRC et al, 1985 (neutral quality). This study was a non-randomized, controlled, two-period cross-over trial that examined the effects on blood pressure and other cardiovascular parameters of three weeks on a reduced Na intake in children. The trial was conducted in Australia. Participants were 21 school children, ages 11 to 14 years, all of whom had BP ≥90th percentile for age on initial BP screening. Subjects followed a low Na or high Na diet for three weeks, and then switched to the alternate Na diet for the subsequent three weeks. Sodium intake was estimated from weekly overnight urine samples and from 24-hour dietary recalls conducted at baseline, three and six weeks. The study showed that there was a three-fold decrease in Na intake on the low Na diet; Na excretion values from final urine samples in each diet period reflected a slightly less than a two-fold difference in Na intake between the high and low Na diets. There was a significant difference between the two diet periods in the level of DBP in the girls ($P< 0.05$). Limitations of the study include the lack of randomization to treatment condition, the very small sample size and lack of statistical power, and the use of self-reported dietary recall data.

Howe et al, 1991 (positive quality). This study was a randomized, two-period crossover trial that examined the effects on blood pressure of four-weeks of a reduced sodium (Na) intake in adolescent children. The trial was conducted in Australia. Participants were 103 adolescent schoolchildren, aged 11 to 15 years. During the low Na period, participants received dietary counseling to lower Na intake. The final analysis was completed on 100 children. Sodium intake was estimated from urine collections and diet histories; both types of measurements confirmed that the intervention reduced sodium intake. The estimated difference in 24-hour sodium intake was ~80mmol per day. Overall, there was no significant difference in BP between the two groups, overall and in any subgroup. The BP changes did not correlate with changes in Na excretion. Strengths of the study are a high follow-up rate. Limitations of the study, which might lead to a spurious null result, include variable adherence (the trial was not a controlled feeding study) and the small number of BP measurements (only one set per week), thereby reducing statistical power.

Lucas A et al, 1988 (negative quality). This report included the results of two randomized controlled parallel trials, that were originally part of a larger five centre feeding study among preterm infants to examine the effects on weight gain during initial hospitalization (27 to 37 days) of different infant formulas, with or without breast milk. The trials were conducted in England. Blood pressure was not measured during this intial in-hospital feeding phase. Since the feeding regimens differed significantly in Na content, BP was measured in 347 infants at 18 months of age to assess the effects on BP of infant feeds differing in sodium content. Study 1 compared BP for preterm infants who had originally been randomized to receive either low Na banked donor breast milk plus standard term infant formula (1.8mmol per kg per day Na intake), vs. a high sodium preterm formula (3.6mmol per kg per day Na intake). Study 2 compared BP for preterm infants who had originally been randomized to receive either low Na banked donor breast milk and standard term infant formula plus expressed maternal breast milk, versus high sodium preterm formula plus expressed maternal breast milk. At 18 months of age, no differences in BP were observed between treatment groups for either study 1 or 2. Strengths of the study included the large sample size. Limitations of the study which could have influenced outcomes include lack of information on how many BP measures were taken; lack of information as to which Korotkoff sounds were used for measures of BP; lack of information on whether BP observers were blinded as to original treatment group. Other limitations included the fact that infant feeds differed in many other aspects in addition to sodium content; that subjects included all preterm infants, both sick and healthy; and that the power calculations for the study were based on the number of infants needed to detect a specific amount of weight gain, and not on hypothesized differences in BP.

Myers JB, 1989 (neutral quality). This study was an RCT that examined the effects on BP in children and adults of a series of two week interventions involving reduced and high sodium diets. The trial was conducted in New Castle, Australia. Participants were 200 (final N=172, 99F, 73 M) healthy normotensive hospital employees and local residents with their families in a community; subjects had a mean age of 36.9 years±1.3 years (range three to 77 years) and had an average body mass and height. Of the 172 who completed the study, 23 persons were <20 years. The study consisted of three periods, each lasting two weeks. In the first study period, subjects were on their usual diet. The second and third study periods involved a randomized cross-over design in which a reduced and a high Na diet were consumed by subjects. Mean urinary sodium excretion in those <20 was 66, 133, and 158 during the lowest, usual and highest Na periods. Mean SBP was 105, 108 and 109mmHg, respectively, while corresponding values for DBP were 62, 67, and 64mmHg. Although there were trends in SBP across the sodium intake levels, no statistical tests were performed for the effects of Na on BP in those person <20 years. Limitations are the small sample size of subjects <18 years of age, the very short duration of intervention, lack of controlled feeding, non-randomized assignment of the usual Na period (always first), and incomplete statistical analyses.

Palacios et al, 2004 (neutral quality). This study was a randomized, two-period crossover trial that examined the effects on sodium retention and BP of three weeks of a high sodium diet and three weeks of a reduced Na diet in adolescents. The trial was conducted in the United States. Participants were 40 female adolescents, aged 11-15 years. This was a controlled feeding study with subjects housed in a metabolic unit and provided with all meals and snacks during the three-week diet phases. The final analysis was completed on 36 children. Sodium intake was estimated from daily urine collections which confirmed that the intervention diets achieved the desired levels of sodium intake. The difference in 24-hour Na excretion between the high and low Na periods was 1.7g per day for Black subjects and 2.4g per day for White subjects. Overall, there was no significant difference in BP between the two diet phases, overall or in any subgroup. The BP changes did not correlate with changes in sodium excretion. Strengths of the study are adherence to the diets since the trial was a controlled feeding study, and frequent measurement of Na excretion (daily) and BP (every other day). Limitations of the study, which might lead to a spurious null result, include the small sample size and high attrition rate (only 23 of the 36 girls completed both diet phases), thereby reducing statistical power.

Pomeranz A et al, 2002 (neutral quality). This study was a randomized, controlled, with crossover trial that examined changes in BP during the first two months of life in neonates receiving low-sodium mineral water (LSMW), high sodium tap water (HSTW), or breast milk. The trial was conducted in Israel. Participants were 58 Jewish newborn term infants from families with no history of hypertension. The initial analysis conducted on 58 infants and final analysis on 38 infants. The intervention involved feeding formula diluted with water containing either LSMW or HSTW for eight weeks; a non-randomized control group consisted of breastfed infants. The group consuming the LSMW formula reverted after eight weeks to consuming the highNa formula. On a weekly basis, SBP, DBP and MAP were recorded during the first eight weeks, and then, at week 24 (six months of age), a follow-up BP measurement was performed. Sodium intake was estimated from only one urine sample with urinary Na:creatinine ratio calculated. In comparison with the low Na intake group and breastfed infants, the high Na intake group exhibited a progressive increase in MAP, SBP and DBP from week four that attained significance at weeks six to eight of study period (P<0.05). When the LSMW reverted to a high-salt intake after eight weeks, their BP values increased towards those observed in the high sodium intake group. Urinary sodium:creatinine ratio was significantly greater in HSTW than in LSMW. Limitations of the study, which might lead to a spurious association, were the small number of participants and the non-random assignment to the control group. Other limitations include uncertain total Na intake in the groups, the pre-post design of the follow-up between weeks eight and 24 in the LSMW, and the loss to follow-up between weeks eight and 24.

Sinaiko et al, 1993 (positive quality). This three-year study was a randomized, controlled, parallel three-arm trial that examined the effects on BP of reduced sodium (Na) intake, potassium (K) supplement, or placebo in adolescents. The trial was conducted in the United States. Participants were 210 adolescents, mean age 13 years with BP at or above the 85th percentile of BP distribution for age. Adolescents were randomly assigned to either a low Na diet (70mmol Na per day), a K supplement (normal diet plus 1mmol per kg KCl per day), or placebo (normal diet plus placebo capsule). Compliance was measured by percent of expected capsule use and by annual 24-hour urinary Na and Na/K ratios. In the low-Na group, 24-hour UNa was changed from 142 to 162mmol for boys, and from 133 to 119 mmol in girls. In the placebo group, 24-hour UNa was changed from 159 to 178 mmol in boys and from 150 to 128 mmol in girls. Change in SBP for the low-Na group was: SBP -1.98±1.3mmHg, and DBP: -4.65±1.91mmHg. The low Na group of girls had a statistically significant negative slope compared with placebo. The slope for boys was similar in all treatment groups.

Strengths of the study are the long term nature of the interventions (three years), and the blinding of BP-observers. Limitations of the study include variable adherence (the trial was not a controlled feeding study), and that neither girls nor boys in the low Na group were successful in reaching the target level of Na intake. In addition, there were few urinary sodium measures (only once every 12 months); and only 59% of boys and 74% of girls had 24-hour UNa measured at year three, though all had 24-hour UNa measured at baseline.

Smith RE et al, 1995 (negative quality). This study was a prospective cohort study begun in infancy to examine the effect of different variables, including anthropometric indices, aspects of feeding practices (including Na intake), and relationship to maternal BP, on the BP of infants. This study was conducted in South Africa. Participants included 684 Sowetan infants from the Birth-to-Ten cohort. At one year of age, an infant feeding history was obtained retrospectively from the mother of each infant, including questions regarding salting practices, and BP was measured in infants and mothers. Results showed that after adjusting for covariates, there was a non-significant trend toward a dose-related response between salt intake and BP, with a positive linear relationship between BP and quantity of salt added to infant foods. A serious limitation of the study is lack of actual measurement of dietary Na intake (estimated only by maternal history), thus numerical estimates of infant Na intake were completely lacking.

Trevisan M et al, 1981 (negative quality). In this report of two studies, one study was an RCT that examined the effects of reduced Na intake on BP. The trial was conducted in the United States. Participants were 21 students in a Seventh Day Adventist boarding high school who were consuming a lacto-ovo vegetarian diet. The students were randomly assigned to a control group (N=9) or the experimental group (N=12), which received moderate salt restriction for 24 days. The experimental study group (N=12) ate meals that lowered sodium intake by ~70% Na from 216 to 72mmol per day. Random 24-hour urines were collected and random duplicate meals were analyzed for Na content, but neither were reported. Blood pressure was measured once at the end of the intervention period. Overall, there was no significant difference in BP between the groups. Limitations of the study which might have led to a spurious null result were the extremely small sample size, the small number of BP measurements, the short duration of the trial, and lack of reported data on the achieved levels of sodium intake.

Tuthill et al, 1985 (positive quality). This study was an RCT examining if a small amount of Na supplementation with food or water influenced BP in a group of female high school students. This trial was conducted in the United States. Subjects were 216 females enrolled in ninth through twelfth grade at a private boarding school. Baseline data was collected for one week prior to supplementation. All subjects took capsules twice per day, under supervision for eight weeks. Group one received a placebo twice a day, group two received two grams of salt capsules midmorning and a placebo in the evening; group three received two grams of salt capsules in the morning. Blood pressure measurements were taken after dinner before capsules and a 24-hour urine collection was done on the same day twice a week for each student. Differences in BP between the treatment groups were not statistically significant (mean differences were in the order of 1.4mmHg at maximum). There was no significant relationship between systolic and diastolic blood pressure and level of Na supplementation (0.8g per day). Strengths of the study include the double blind intervention design, and large sample size. A significant weakness of the study, however, was the lack of statistical power. The original power calculations were based on combining data from two schools, however the authors chose to analyze the data from each school separately. With the smaller sample size only a 2.5mmHg difference in BP between groups could be detected, whereas the actual mean differences were in the order of 1.4mmHg at maximum.

Whitten CF and Stewart RA, 1980 (neutral quality). This study was a non-randomized trial in which infants at three months of age were assigned to receive low Na foods (2mEq of Na per 100kcal) or high Na foods (9mEq of Na per 100kcal) for five months. Long-term effects were assessed at eight years of age. This study was conducted in the United States. Subjects were 27 healthy three-month old African American male infants. Follow-up data were collected one, three and five months later. At each of these timepoints, the infants were admitted to the hospital for three days of measurements, includingBP and urinary sodium excretion. At five months, mean urine excretion was 11mmol per day and 55mmol per day in the low and high groups. There were non-significant trends after the five month intervention and at eight years such that SBP was greater in the high sodium group compared to the low sodium group (after five months of intervention: mean SBP of 90 vs. 88mmHg; at eight years, 105 vs.103mmHg). Limitations of the study which might lead to a spurious result were the very small sample size, uncertain allocation process, and uncertain analytic strategy. Strengths of the study include the large number of measurements per individual and extended follow-up period.

Overview Table Key
*** Subjects were defined as salt sensitive if BP at end of run-in period (usual diet) was higher than on the low Na diet but less than on the high Na diet. N indicates number of participants, and the number in bracket represents the number of participants in low-salt and control group, respectively; UNa, urinary sodium; Δ salt intake, net change in salt intake; Δ SBP, net change in systolic BP; Δ DBP: net change in diastolic BP; NR: not reported. SM = sphygmomanometer. * The Myers study (1989) included adults and children (N=172; ages 3-77yrs), but in the He FJ meta-analysis, only the child participants (N=23, mean age 11yrs) were included in the analysis. ** Tuthill- Problem with lack of statistical power: The authors intended to combine the two campus' data and the power to determine a difference of 1.5mmHg would have required the total data set to be combined for an N of 214 (71 in each Rx group). However, they had to analyze each campus separately, so given the smaller sample size only a 2.5mmHg BP difference would be detectable. The actual mean BP differences were in the order of 1.4mmHg at maximum.

View table in new window

Author, Year, Study Design, Class, Rating	Participants/Location	Study Duration	Intervention Procedure	BP Measurement; Sodium Intake Measurement	Outcome (BP values; mmHg)
Brion MJ, Ness AR et al, 2008 Study Design: Prospective cohort study Class: B Rating:	N=533; Age: Four months. N=710; Age: Eight months. 1,394 infants have data from at least one visit. Final analyses on children with complete information on all confounders. Location: United Kingdom.		Sodium intake was measured in infancy and at seven years; BP measured at seven years. The Avon Longitudinal Study of Parents and Children.	BP measured by Dinamapp 9301. Two readings taken and the mean for each measure calculated. Sodium intake estimated from one-day food diary at four months and three day diary at eight months. Mean sodium intake at: Four months: 7.2 mmol/day Eight months: 23.1 mmol/day.	Difference in salt intake (from food diary) at four months was -0.4 mmol/day between Q1 and Q4 BP. After minimal adjustment (age, sex, energy) sodium intake at four months (but not at eight months or seven years) was positively associated with SBP at seven years 0.98mmHg; P=0.02. An ↑ in E-adjusted Na at four

					months of 9mmol/day was associated with an ↑ in SBP at seven years of 4.0mmHg BP-lower with Low-Na (four months). **Stat-SIG.**
Calabrese EJ, Tuthill RW et al, 1985 Study Design: Randomized controlled trial Class: A Rating:	N=153 (51+102). Mean age: Nine years, 51% boys. Mean BP: 99/57mmHg. Location: United States.	Duration:12 weeks (three months).	Bottled water with varied salt content (110 or 10mg/L) provided for children's family and school classrooms.	BP was measured with mercury SM; Korotkoff 1 and 5 for SBP and DBP. Mean of three readings used in analysis. Sodium intake estimated from first morning urine specimens (1 x month), and from weekly 48 hour diet records kept by the children.	Δ Salt intake: -11.70% (spot UNa). UNa Δ from 141 to 128mmol/L in the Low-Na group, and from 121 to 124mmol/L in the control group. (Note: Low-Na group only -4mmol/L less than High-Na group at end of study). Net difference in BP: Δ SBP: -0.80 ±0.80 Δ DBP: -1.50 ±1.65 **BP-reduced for all, but Stat-SIG for girls only.**
Cooper R, van Horn L et al, 1984 Study Design: Randomized, controlled, crossover trial Class: A Rating:	N=113. Mean age: 16 years, 47% boys. Mean SBP: 109/61mmHg Location: United States.	Five-day washout. BP-observer blind. Duration: 24 days.	Control diet: 200 mmol/day salt; Low salt diet: ~60mmol/day salt.	First BP measured with mercury SM. Second and third BP measured with random-zero SM. Mean of second and third BP used. Sodium intake estimated from overnight urine samples.	Δ Salt intake: -57.68% (overnight UNa) Net difference in BP: Δ SBP: -0.60±0.70 Δ DBP: -1.40±1.00. **BP-reduced; not stat-sig.**
Ellison RC, Capper AL et al, 1989 Study Design: Non-randomized, concurrently controlled, longitudinal investigation, with the applications of	N=309 for intervention year; N=341 for control year. Mean age: 15 years, 49% male, 77% white. Mean BP: 107/64mmHg. Location: United States.	~Five month washout BP-observer blind. Duration: Six months.	Low-salt year: Salt intake reduced by 15-20% via changes in food purchasing and preparation at boarding school.	Weekly BP measured x 3 by students using a Dinamap 845 device connected to a computer. Mean of second and third BP measures used. Sodium intake estimated from food diaries: 4.5/subject at base and follow up.	Δ Salt intake: -16.20% (from food diary). Net difference in BP: Δ SBP: -1.70±0.56 Δ DBP: -1.50±0.46. **BP-reduced; Stat-Sig.**

the intervention in each of two boarding high schools in alternate school years. Class: C Rating:					
Geleijnse JM, Hofman A et al, 1997 Study Design: Randomized trial Class: A Rating:	N=167. 71 from infant low Na group; 96 from infant control group. This was 35% of the original cohort of 476. Location: The Netherlands.	15 year follow-up study of the Hofman et al, (1983) infant study subjects.	The intervention had occurred during the first six months of life, 15 years earlier.	BP measured with the Dinamap 8100 Monitor; four measures of BP and HR taken; last three measures averaged. Sodium intake estimated from spot urine collection in the infant RCT. Overnight urine samples were collected at the 15 year follow up.	A difference in Na intake of 8.8mmol/day between the randomized groups corresponded to a -3.6mmHg lower SBP in children randomized to the low-Na group for the first six month of life. After multivariate adjustment for potential confounders, SBP was -3.6mmHg lower (95%CI,-6.6 to -0.5; P=0.02) and DBP was -2.2mmHg lower (95%CI,-4.5 to 0.2; P=0.08) than Control. For subjects with mean HR >median: Adjusted SBP at follow up was -6.0mmHg (95%CI,-10.5 to -1.5.2; P<0.01).; and adjusted DBP was -4.8mmHg (95%CI,-8.7 to -0.9; P<0.01) * SBP-lower with

					low Na. **Statistically significant.**
Gillum RF, Elmer PJ et al, 1981 Study Design: Randomized controlled trial Class: A Rating:	N=51 (15+36). Age: Six to nine years, 54% boys. BP >95th percentile for age/sex, but <130/90mmHg. Mean BP: 114/68. Location: United States.	Duration: One year.	Children ahd parents attended four biweekly sessions; then bimonthly sessions. Goal for sodium intake: 70mmol/day.	BP measured at home; random-zero SM. DBP = Korotkoff fourth sound. BP-observer blind. Sodium intake estimated from overnight urine samples. *[*Note: Compliance with diet records and urine collections was a problem in the intervention group.]*	Overnight UNa+ at one year follow up was significantly lower for active participants of the low-sodium group (87mmol/24-hours) compared to dropouts (130mmol/24-hours) and controls (133mmol/24-hours). Δ Salt intake: –1.36% between Intervention and control groups (30 vs 31 mmol/ 10hr). For Intervention (attenders) minus Controls, the diff in BP at 1 year was: Δ SBP: 3.00±2.61 Δ DBP: 2.90±5.79. **Not Statistically Signif.**
Hofman A, Hazebroek A et al, 1983 Study Design: Double blind randomized trial Class: A Rating:	N=466 (225+241). Newborn, 51% boys. Location: The Netherlands.	Double-blind. Duration: Six months.	Formula and foods provided to subjects. Control formula contained Na that was usual for Dutch formula during the study period. Low Na formula had one-third the sodium as the control formula.	SBP measured in weeks one, five, nine, 13, 17, 21, 25) with a Doppler ultrasound device connected to a random-zero SM. Mean of three readings used. BP observer blind. Sodium intake estimated from three casual urine samples (weeks five, 13, 21) and from the food given to baby, with allowance for the sodium content of breast milk.	Δ Salt intake: -51.10% (from spot UNa). Sodium intake estimated from three casual urine samples (weeks five, 13, 21) was 11.1 mmol/L for the low-Na group, and 22.7 mmol/L for the normal Na group. Δ SBP: -2.00±0.92 (P=0.03). **BP-reduced **(Stat-SIG).**
Howe PR, Cobiac L et al, 1991 Study Design: Randomized controlled trial with crossover Class: A Rating:	N=100. Age: 11-14 years, 52% boys. Equal number from top, middle, and bottom deciles of BP distribution. Mean BP: 115/60mmHg. Location: Australia.	Duration: Four weeks.	Child/parent: weekly diet counseling; low-salt bread during low salt period; salt packets provided in control period. Goal for low-sodium diet: <75mmol/day. For high sodium diet: >150mmol/L.	BP measured with Dinamap monitors; mean of the second and third of three BP readings used in the analysis. BP-observer blind. Sodium intake estimated from spot urine samples.	Δ salt intake: -42.13% (spot U Na/Cr ratio); Difference in UNa was 81mmol/day between end of low and high Na periods. Net difference in BP: Δ SBP: -0.97±0.68 Δ DBP: -0.56±0.71 **BP-reduced, but Not stat-sig.**

Howe PR, Jureidini KF et al, 1985 Study Design: Non-randomized control trial Class: C Rating:	N=21. Age: 11-14 years, 52% boys. BP≥90th percentile adjusted for age and height. Mean BP: 119/78mmHg. Location: Australia.	Duration: Three weeks.	Parents and children instructed by RD on diet.	BP measured with mercury SM. Korotkoff sound 1 and 4 = SBP and DBP, respectively. Sodium intake estimated from overnight urine samples.	Δ Salt intake: -43.25% (overnight UNa). Net difference in BP: Δ SBP: 0±2.32 Δ DBP: -1.30±1.78. ' **BP-reduced **(Stat-SIG).**
Lucas A, Morley R et al, 1988 Study Design: Randomized trial Class: A Rating:	N=347 preterm infants. Healthy and sick; Five center study. Note: There were four different trials (intervention arms) in the original RCT trial. At this 18-month follow up, the four groups were condensed to two (Study 1 and Study 2). This was done since there was no difference in BP between infants fed donor breast milk or regular formula. Combining the groups would allow them to compare BP between babies fed 'Low-Na' vs. 'Hi Na' diets during their first month of life. Location: United Kingdom.	This was an 18-month follow up of an randomized, parallel, clinical trial. Initial trial duration 27-37 days (while preterm baby was still hospitalized). Follow up with BP measurement at 18 months age.	Random assignment to feeds until hospital discharge (27-37 d): Study 1 (N=110) compared BP for infants originally randomized to either: (1a) Hi-Na Preterm formula, which provided 3.6 (0.07)mmol/kg/day Na; or (1b) Banked donor breast milk (BDBM) and a regular Term infant formula, which provided 1.8 (0.06)mmol/kg/day Na. Study 2 (N=121) compared BP for infants originally randomized to either: (2a) Hi-Na Preterm formula plus expressed maternal breast milk (EMBM), which provided 2.8 (0.07)mmol/kg/day Na; or(2b) Banked donor breast milk	SBP and DBP measured with standard mercury SM. Number of measures unknown. Sodium content of the standard infant formula (8.3mmol/L), pre-term formula (19.6mmol/L); banked donor breast milk (7.2mmol/L), and expressed breast milk (11mmol/L) was determined.	Feeding a high sodium preterm formula in the neonatal period did not influence BP at 18 months of age. **BP-no difference at 18 months.** Age between feeding groups. Study 1: *Low Na:* SBP 97.1 (1.3); DBP 65.4 (1.1); *Hi-Na:* SBP 96.6 (1.3); DBP 66.1 (1.1) Study 2: *Low Na:* SBP 97.8 (0.9); DBP 65.8 (0.7); *Hi-Na:* SBP 96.6 (0.9); DBP 65.5 (0.7) ***Note: The power calculations for this study (described in the 1984 report) were based on the number needed to detect a specific amount of weight gain (g/kg/day) and not on BP.***

			(BDBM) and a regular Term infant formula, plus EMBM which provided 1.8 (0.8)mmol/kg/day Na.		
Myers JB, 1989 Study Design: Randomized trial Class: A Rating:	N=23 <18 years old; Mean age: 11 years. 40% boys. Mean BP: 108/67mmHg . (Adults in this study not included.) Location: Australia.	Two- week run-in on usual diet; then crossover periods: Two weeks on High-Na diet Two weeks on Low-Na diet. *[Note: Very short intervention (two week on each diet).]*	RD advised subjects on study diet based on the diet history and 24-hour UNa	BP measured with a mercury SM with observers blind as to diet of subjects. Sodium intake estimated from 24-hour urine samples.	Δ Salt intake: -58.23% (from 24-hour UNa); UNa excretion was 66mmol/24-hour on the Low Na diet; vs. 158mmol/L on the High Na diet (and 133 on the usual diet). Net difference in BP between diets for all children (N=23): Δ SBP: -3.74 ±1.98 Δ DBP: -1.70±2.17. Net difference in BP between diet phases for salt sensitive children*** (N=5): Δ SBP: -10±5 (P=0.06) Δ DBP: -15±1 (P<0.005). **BP-reduced on Low Na.** The difference in BP on Low vs. High Na was statistically significant for all subjects (age three-77 years), but it is not clear if the differences were stat-sig for the <18 year group.
Palacios C, Wigertz K et al, 2004 Study Design: Randomized crossover trial Class: A Rating:	N=36. Age: 11–15 years. All girls, 39% white; 61% Black. Mean BP: 113/57mmHg. Location: United States.	Two-week washout in between. Duration: Three weeks. Subjects housed in metabolic unit.	All foods and drinks provided to children; Strict supervision to ensure compliance. Low salt diet: 43mmol/day Na. Control diet: 174mmol/day Na.	Supine BP was measured using mercury SM. K 1 and 5 were taken for SBP and DBP, respectively. Sodium intake estimated from daily 24-hour urine samples, and from six-day diet records.	Δ Salt intake: -70.8%. 24-hour UNa was reduced from 140.8 to 41.1mmol/24-hours. Na excretion was similar in W vs. B girls at low sodium intakes, but significantly lower in B vs. W girls at high Na intake. Net difference in BP between low and high sodium diets: Δ SBP: -2.43±2.72 Δ DBP: 1.06±1.98. SBP and DBP ↓ significantly from

					baseline to end of follow up for**both** diets, and for both WF and BF: SBP: 108.6 to >98.7 WF; Low Na DBP: 63.0 to >49.8 WF; Low Na SBP: 107.2 to >101.0 BF; Low Na DBP: 51.8 to >49.5 BF: Low Na. SBP: 108.1 to >98.8 WF: High Na DBP: 47.8 to >45.6 WF: High Na SBP: 102.8 to >97.6 BF; High Na DBP: 53.4 to >49.6 BF; High Na *[Note: This may have been due to the weight loss that occurred during the trial in both groups.]* *BP was significantly lower on both diets; but NS differences **between** the two diets*
Pomeranz A, Dolfin T et al, 2002 Study Design: Randomized controlled trial with crossover Class: A Rating:	N=58 (25+33). Newborns in the intervention; 15 breast fed infants served as controls. Location: Israel.	BP-observer blind. Duration: Eight week intervention trial; Follow up to age six months.	58 infants were randomly assigned to one of twogroups: Formula diluted with low Na spring water; or Formula diluted with high sodium tap water for eight weeks. After the eight week intervention, all infants had formula diluted with High Na tap water to age six months. NMa intake estimated to be 9.5mmol/L (Low-Na group), and 16.6mmol/L (High Na group).	BP measured with the Dinamap 8100 Monitor, (BP and pulse by Doppler). BP measured at home during sleep. Sodium intake estimated from flame photometry analysis of formula powder and of the waters used to dilute the formula.	Δ Salt intake: -53.85% (spot UNa/Cr ratio). Net difference in BP between diets for all subjects: Δ SBP: -5.30±2.06. * At eight weeks, SBP, DBP and MAP were significantly greater in the High-Na group than in the Low-Na group or in the breast fed controls. **At 24 weeks, the High-Na group still had SBP, DBP and MAP statistically higher than the breast fed controls.** BP for the original Low-Na group (which since age eight weeks had been switched to High-Na water) was still lower than the High-Na group (but not a statistically significant difference). **BP was reduced on Low-Na compared with High-Na at eight weeks of age. Stat-Sig.**

Sinaiko A, Gomez-Marin O et al, 1993 Study Design: Randomized controlled trial Class: A Rating: ⊕	N=139 (70+69) students in public schools. Mean age: 13 years, 50% M; 88% white. BP in the top 15th percentile of BP distribution. Mean BP: 114/64mmHg Location: United States.	Duration: Three years.	Diet counseling by RD. Neither boys nor girls reached the target levels of sodium intake for the low sodium period.	Random-zero SM used; Means of two measures; K1 and K5 for SBP /DBP. BP-observer blind. Sodium intake estimated from 24-hour urine samples, but only 59% of boys and 74% of girls had 24-hour UNa at year three. Compliance problem - boys.	Δ Salt intake: 0.0337% (24-hour UNa); -16.2 % from food diaries. (UNa ↑ for boys in both Rx groups; but ↓ for girls in the low Na group (133 to 119mmol/day). Overall Δ in BP: Δ SBP: -1.98±1.32 Δ DBP: -4.65±1.91. **BP-reduced for Girls - Stat-SIG negative slope on Low Na vs Ctrl.****
Smith RE, Kok A et al, 1995 Study Design: Prospective cohort Class: B Rating: ⊖	N=972 infants at one year. Birth to Ten cohort of Seweten infants. Location: South Africa.		Examined influence of weight, length, upper arm circumference, age formula feeds started, volume of formula feeds, and maternal BP on child's BP at 18 months of age.	SBP measured at one year of age with hand held aneroid SM and a Doppler ultrasound system. Sodium intake estimated from diet questionnaires completed by the mother.	No quantitative measure of Na intake. In the multivariate analysis, 29.3% of the variance forSBP was accounted for by weight (P=0.0001); upper arm circumference (P=0.0007); age formula started (P=0.0096); length (P=0.0346); and volume of formula feeds (P=0.0598). **Amount of salt added to diet approached stat-sig.** **(P=0.0751)** **In the multivariate analysis, variables were entered into the model and factors which did not predict SBP were removed one at a time.*
Trevisan M, Cooper R et al, 1981 Study Design: Study 1: Cross-sectional; Study 2: Randomized trial Class: A Rating: ⊖	N=21 (12+9). Age: 11-15 years. Mean SBP: 109mmHg. Location: United States.	BP-observer blind. Duration: 24 days.	Children followed either control diet or a diet ~70% lower in sodium.	BP measured with VITA-STAT (automatic device); Mean of two readings, one minute apart. Sodium intake estimated from 24-hour urine samples.	Δ Salt intake: (not stated). Net difference in BP: Δ SBP: -1.25±4.96 Δ DBP: NR. **SBP-reduced; Stat-Sig.**
Tuthill RW and Calabrese EJ, 1985 Study Design: Randomized control trial	N=216. High School girls from two campuses of private boarding schools (Grades 9-12). *[Note: Only 47.6% of eligible students at Campus 1, and 32.3% at campus 2 volunteered for the study)* Location: United	Duration: Eight weeks. One week base-data. Eight weeks follow up data.	Three treatment groups took capsules BID: Placebo (dextrose). 0.8g sodium (2g salt) in a.m. with water; 0.8g sodium (2g salt) in p.m. with dinner.	BP was measured in duplicate, twice a week. (Device used not stated). Sodium intake estimated from 24-hour urine samples, twice weekly.	Δ Salt intake ~ **-56% for campus 1; but unable to estimate for campus 2 (data in figure form only).** **Differences in BP between Rx groups were not statistically significant.**

Class: A Rating:	States. Note: This is not a trial of salt reduction.			Note: There was a rapid rise in BP in the first several weeks which corresponded to the rapid increase in Na excretion that occurred at the same time, probably reflecting a significant Δ in diet as students began their semester at these private boarding schools.	Mean BP differences were in the order of 1.4mmHg at max. There was no effect on BP of 0.8g sodium added to the usual dietary intake of healthy teenage girls. UNa measures showed that the desired sodium difference between RX groups was achieved. **But the study was underpowered.**** The authors intended to combine the data from the two schools, since the power to detect a BP difference of 1.5mmHg required the total data set with N=214 (71 per Rx). But they had to analyze each campus separately, so with this smaller sample size only a 2.5mmHg BP diff could be detected. The actual mean BP differences were in the order of 1.4mmHg at maximum. **No BP lowering with low Na.**
Whitten CF and Stewart RA, 1980 Study Design: Prospective cohort Class: C Rating:	N=27 (13+14). Age: Three months. All African-American boys. Location: United States.	BP-observer blind. Duration: Five months.	All infant foods were provided; Na intake was 9.25 (control) and 1.93mmol/100kcal (low-salt group).	Air Shield BP Monitor used; Automatic reading every five minutes. BP measured six to 12 x during the three-day hospital stay. Only readings taken during sleep and ~one hour after feeding used in analysis. Sodium intake estimated from 24-hour urine samples.	Δ Salt intake: -79.38% (from 24-h UNa). Δ SBP: –2.00±2.13. * Difference in BP between groups was not significant at eight months and at eigh years, but the study may have been insufficiently powered to detect such effects. *** Decreased SBP; NS.**

Research Design and Implementation Rating Summary
For a summary of the Research Design and Implementation Rating results, click here.

Worksheets

Brion MJ, Ness AR, Davey Smith G, Emmett P, Rogers I, Whincup P, Lawlor DA. Sodium intake in infancy and blood pressure at seven years: Findings from the Avon Longitudinal Study of Parents and Children. *Eur J Clin Nutr.* 2008 Oct; 62 (10): 1,162-1,169.

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